

REMARKS/ARGUMENTS

Claims 1-29 are pending in the instant application. Claims 1-29 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as the invention. Claims 1-7, 9, 12, 16-18, 21, 23, 27, and 28 stand rejected under 35 U.S.C. §102(e) as being anticipated by United States Patent No. 6,426,058 to Pines et al. Claims 1-7, 9, 12, 16-18, 21, 23, 27, and 28 stand rejected under 35 U.S.C. §102(e) as being anticipated by United States Patent No. 6,278,893 to Ardenkjaer-Larson et al. Claims 1-29 stand rejected under 35 U.S.C. §102(e) as being anticipated by United States Patent No. 6,574,496 to Golman et al. Claims 8, 14, 15, 19, 20, 24-26, and 29 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Pines et al. Claims 10, 11, and 13 stand rejected under 35 U.S.C. §103(a) as being upatentable over Pines in view of United States Patent No. 6,103,492 to Yu. These rejections are respectfully traversed. Reconsideration is respectfully requested.

First, Applicants would like to point out that the incorrect page 1 was included in the PCT publication. Examination of the page 1 published with our files indicates that the page 1 of another applicant's specification was incorrectly included in our specification. The correct page 1 as originally filed by Applicants is enclosed. Applicants request that this corrected page 1 be substituted for the erroneous page 1.

Claims 1-29 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as the invention. This rejection is respectfully traversed.

The Examiner objects to the claims for being

“generally narrative and indefinite, failing to conform with current US practice. They appear to be a literal translation into English from a

**foreign document and are replete with grammatical and idiomatic errors.
(For example, the spelling of “polarisation” should be –polarization).**

The Examiner's objections are unclear. Applicants respectfully request the Examiner to particularly identify those passages which are “replete with grammatical and idiomatic errors”. Applicants herewith amended the first step of claim 1 so as to be consistent with US practice in defining the present invention. This amendment is based on preferences customary in US patent practice and is in no way intended to diminish the scope of the claims. Additionally, a minor typographical error has been corrected in claims 2 and 9. Claim 15 has been amended to correct an unidentified antecedent basis concern. Applicants' undersigned counsel stands ready to discuss any particular concerns the Examiner has with respect to this rejection at the Examiner's convenience.

Applicants respectfully submit that the Examiner's objection to the spelling of the term ‘polarisation’ is unnecessary. The terms ‘polarization’ and ‘polarisation’ are both accepted spellings of the same terms. ‘Polarisation’ is the accepted spelling in, for example, the United Kingdom, as well as other English-speaking countries. On page 900 of Merriam-Webster's Collegiate Dictionary, Tenth Edition, photocopy provided, notes that ‘polarise’ is simply the British variation of ‘polarize’. Applicants submit that those of ordinary skill in the art in this country will recognize the terms ‘polarisation’ and ‘polarization’ as having the same meaning. Reconsideration is respectfully requested.

The Examiner states that claim 1 is unclear as to how the assay is performed, e.g. whether a sample is required, what steps are required in the assay. The term “assay reagent” is defined on page 4 lines 4-24 of the instant application. Examples of some assays envisaged by the invention are described on page 7 lines 13-28. Claim 1 does not include all the steps of a particular assay as the method of claim 1 is intended to be applicable to a range of known *in vitro* assays as described in the description. Applicants respectfully submit that the person skilled in the art would be well-acquainted with the various assays and assay

reagents described and would immediately know what is intended by claim 1 when read in conjunction with the description.

Also with respect to claim 1, the Examiner states that it is unclear what steps are required to generate further assay results. Applicants respectfully submit that a person skilled in the art would know that the spectral data generated by NMR analysis can be used in the generation of further data such as to give information about the structure of a compound (see page 18 line 12). It is therefore not necessary to limit the claim by including a specific method to generate further assay results.

The Examiner objects to the term "known assay techniques" in claim 15. This term is qualified in claim 15 by the words "without hyperpolarisation". Therefore the skilled person would know that the comparison referred to in claim 15 is between the same assay with and without polarization. As mentioned already, some examples of suitable assays of the invention are described on page 7 lines 13-28.

The Examiner has objected to the term "other suitable container" in claim 28. Applicants respectfully submit that a person skilled in the art of hyperpolarising gases would immediately know that a variety of containers would be suitable for both containing the assay reagents and carrying out the hyperpolarisation, a well and a vial being suitable examples. The scope of the term "other suitable container" should therefore not present any difficulty for the person skilled in the art.

In view of the hereinabove amendments and remarks, Applicants respectfully submit that the Examiner's objections have been either obviated or traversed. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 1-7, 9, 12, 16-18, 21, 23, 27 and 28 stand rejected as being anticipated by Pines *et al* (US 6426058). This rejection is respectfully traversed.

Pines relates to nuclear magnetic resonance (NMR) spectroscopy and imaging in which hyperpolarised gases are used to enhance and improve the spectroscopy and imaging. The Examiner states that Pines discloses using an assay reagent (column 12 lines 6-27) containing at least one NMR active nucleus (column 15 lines 37-41) to perform an assay, and hyperpolarizing at least one NMR active nucleus (column 15 lines 43-45) and analyzing the assay reagent and/or the assay by NMR and optionally using the NMR data obtained to generated further assay results (column 18 lines 61-64). Applicants respectfully submit that Pines fails to disclose an assay as defined in the present invention on page 4 lines 6-7, i.e. one "...in which a physical or chemical change involving a biological species is observed". No physical or chemical change is observed in the method disclosed in Pines and as such the method is not an assay as encompassed by claim 1 of the present invention.

Therefore, as Pines fails to disclose an assay for use in hyperpolarization, Pines fails to disclose each and every element of the cited claims. Applicants submit that claims 1-7, 9, 12, 16-18, 21, 23, 27 and 28 are thus novel over Pines. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-7, 9, 12, 16-18, 21-23, 27 and 28 stand rejected as being anticipated by Ardenkjaer-Larsen *et al* (US 6278893). This rejection is respectfully traversed.

Ardenkjaer-Larsen relates to a method of magnetic resonance investigation of a sample wherein an NMR active agent is administered to said sample. Applicants respectfully submit that the method of Ardenkjaer-Larsen, as argued against Pines hereinabove, is not an assay as encompassed by claim 1 of the present invention as it does not result in a physical or chemical change involving a biological species.

Therefore, as Ardenkjaer-Larsen fails to disclose an assay as presently claimed, Applicants respectfully submit that the present invention is novel thereover. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-29 stand rejected as being anticipated by Golman *et al* (US 6574496). This rejection is respectfully traversed.

The method of Golman involves the administration of a magnetic resonance imaging agent to a sample and subsequently detecting signals from the imaging agent. As discussed for Pines and Ardenkjaer-Larsen above, Golman fails to disclose a method of magnetic resonance investigation involving an assay, as defined in the present invention, which results in a physical or chemical change involving a biological species.

Applicants again submit, as Golman fails to disclose each and every element of the claimed invention, the present invention is novel thereover. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 8, 14, 15, 19, 20, 24-26 and 29 have been rejected under 35 U.S.C. §103(a) as being obvious over Pines *et al*. This rejection is respectfully traversed.

The Examiner contends that although the content of these claims is not explicitly disclosed by Pines, that it would have been obvious to modify the teachings of Pines to arrive at the content of these claims. As discussed above in the section relating to 35 USC § 102, Pines fails to disclose an assay as defined in the present invention. Moreover, Pines fails to disclose, teach, or suggest an assay as is presently claimed. As Pines fails to disclose, teach, or suggest the present invention, Applicants respectfully submit that the present invention is patentably distinct thereover. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 10, 11 and 13 have been rejected under 35 U.S.C. §103(a) as being obvious over Pines *et al* in view of Yu (US 6103492).

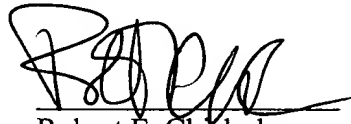
As Applicants have already demonstrated the patentability of the intervening base claims over the prior art, Applicants respectfully submit that all of their dependent claims, including claims 10, 11, and 13, are likewise patentable. Reconsideration and withdrawal of the rejection are respectfully requested.

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In view of the amendments and remarks hereinabove, Applicants respectfully submit that the present invention, including claims 1-29, are patentably distinct over the prior art. Favorable action thereon is respectfully requested.

Should the Examiner have any questions with respect to the foregoing, Applicants' undersigned counsel may be contacted at the telephone number listed below.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'R. F. Chisholm', written over a horizontal line.

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IN VITRO NMR METHOD

This invention is concerned with nuclear magnetic resonance spectroscopy. The technique involves observing the spectrum of a NMR active nuclear species, particularly a hyperpolarised nucleus, in order to obtain information about the environment in which the species is present. The spectra of NMR active nuclei vary depending on their environment, as reported in the literature (PNAS, 93, 12932-6, 1996).

Noble gases having non-zero nuclear spin can be hyperpolarised, i.e. have their polarisation enhanced over the equilibrium polarisation, e.g. by the use of circularly polarised light. Preferred techniques for hyperpolarisation include spin exchange with an optically pumped alkali metal vapour and metastability exchange. Noble gases to which this technique can be applied include ^3He and ^{129}Xe . As described by M S Albert *et al* in US Patent 5,545,396, the technique can be used to prepare hyperpolarised noble gases which can then be administered by inhalation for magnetic resonance imaging of the human body.

It is known that the hyperpolarisation of a noble gas can be transferred to another NMR active species by physical contact. Thus WO 97/37239 (Lawrence Berkeley National Laboratory) describes a method which involves: contacting a sample containing an NMR active nucleus with a hyperpolarised noble gas; scanning the sample using nuclear magnetic resonance spectroscopy, magnetic resonance imaging, or both, in order to detect the NMR active nucleus. WO 98/30918 (Nycomed Imaging AS) relates to *ex-vivo* dynamic nuclear polarisation (DNP) of the NMR active nuclei of an MR imaging agent by a hyperpolarised gas where the gas is separated from the MR imaging agent prior to administration to the body.

The present invention concerns the hyperpolarisation of one or more NMR active nuclei of compounds involved in an assay. The hyperpolarisation may be carried out using a variety of techniques, such as polarisation transfer from a noble gas, "Brute force", DNP (WO 98/58272, Nycomed Imaging AS) and the para hydrogen ($p\text{-H}_2$) method, as explained below.

The transfer of hyperpolarisation according to the present invention may be achieved by using a hyperpolarised noble gas, preferably ^3He or ^{129}Xe , or a mixture of such gases, to effect

our remnant. Lith. *nilis* castle (1716). 1. *car*: the interior.